Newly developed surface modification punches treated with allying techniques reduce sticking during the manufacture of ibuprofen tablets

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Abstract

Sticking is a serious problem during the manufacturing process of tablets. In order to prevent this, we used alloying techniques to prepare metal hardening (MH) and electron beam processing infinite product (EIP) punches with rougher asperity of surfaces than a hard chrome plated (HCr) punch. This study evaluated the anti-sticking properties of the MH and EIP punches compared to the HCr punch, using quantitative scraper force measurements and visual observation, for the manufacture of ibuprofen (Ibu) tablets. The anti-sticking property mechanism of the MH and EIP punches was also confirmed. The amount of Ibu adhering to the punch surface was 66% lower for the MH and EIP punches than for the HCr punch, suggesting a superior anti-sticking property of the MH and EIP punches. The scraper force of the HCr punch was 2.60–4.28 N, while that for the MH and EIP punches was 0.54–1.64 N and 0.42–1.33 N, respectively. The result of X-ray photoelectron spectroscopy suggested that the anti-sticking property of the EIP punch was attributed by the rough asperity as well as existence of low friction substance carbon fluoride on the punch surface. In conclusion, this study provides new evidence for the mechanisms behind the superior anti-sticking property of the MH and EIP punches.

Keywords: Tableting, Sticking, Scraper force, Ibuprofen, Surface modification
1. Introduction

Sticking is one of the most serious problems to occur during the tablet manufacturing process because it induces roughness or cracks on the tablet surface, resulting in deterioration in tablet productivity and appearance. Sticking can be caused by an excess of water in the granules or powder (Danjo et al., 1997), a lack of lubricant (Roberts et al., 2004a), or punch surface conditions (Roberts et al., 2004b). In order to prevent sticking, several approaches have been attempted including increasing the mixing time or the amount of lubricant in the formulation (Mitrevej et al., 1982, Waimer, et al., 1999), making changes to the tableting compression (Roberts et al., 2004b, Waimer, et al., 1999), cleaning and polishing the punch surface (Waimer, et al., 1999), and adding a hard chrome plating (HCr) or other coating to the punch surface (Roberts et al., 2003, Schumann et al., 1992, Watanabe et al., 1998).

After the countermeasures are treated, tableting with no sticking problems can be performed temporarily; however, sticking will occur again. Therefore, these countermeasures do not solve the sticking problem fundamentally. In addition, the coating method may be insufficient or leave a risk of peeling during the compression process. Hence, an alternative method to prevent sticking in the tableting process is required.

Previously, we designed two types of punches, the metal hardening (MH) punch and the electron beam processing infinite product (EIP) punch, which both have their surfaces modified by alloying techniques. Figure 1 shows a schematic diagram of the surface treatment and laser microscopy images of the punch surfaces. Generally, the surface of an HCr punch is flat and smooth, while
that of the MH punch made from a discharge of tungsten carbide (alloying process), is rough, with an asperity range of 0.5–5.0 μm (Fig. 1a and 1b). This roughness can be controlled at the time of the discharge alloying process by varying the pulsed electrical current (Uemura et al., 2007). The EIP punch is made by the molten alloying of a metal with a low friction property such as calcium fluoride (Fig. 1c). Thus, various types of EIP punches can be prepared based on the characteristics of the metal itself and/or combinations without an electrode. Although the surface is still irregular and rough, it is slightly smoother than that of the MH punch (Fig. 1d).

Previously, Uemura et al. reported that tablet sticking on a rotary tablet machine was prevented for the MH punch compared to the HCr punch when compressing powder mixtures composed of ascorbic acid, corn starch, and small amounts of magnesium stearate (Uemura et al., 2007). Further, when a sodium fluoride-treated EIP (EIP-NaF) punch was used to compress powder mixtures composed of ibuprofen, mannitol, and colloidal silicon dioxide with a rotary tablet machine, no powder adhesion on the surface of the punch was observed after tableting for 80 min, compared with powder adhesion on the surface of the HCr punch and chromium nitride-plated punch within 44 and 80 min, respectively (Sekine et al., 2010). Although these reports suggest that both MH and EIP-NaF punches might overcome the sticking problem, their ability to do this has been evaluated only visually, so further quantitative evaluation is required. In addition, the elucidation of the anti-sticking mechanisms of the MH and EIP punches is also required.
Therefore, in the present study, we quantitatively evaluated the sticking by assessing the scraper force between the tablet and the surface of the lower punch during the tableting process as a conventional method described previously (Flament et al., 2002, Wang et al., 2004, Shibata et al., 2005). The anti-sticking properties of two alloyed punches, MH and EIP, against granules containing ibuprofen as a model sticking formula were evaluated both by scraper force measurement and visual observation. In addition, the internal friction coefficient was also evaluated to elucidate the anti-sticking mechanism of the two punches.
2. Materials and Methods

2.1. Materials

We prepared a hard chrome (HCr)-plated punch, a metal hardening (MH) punch with an asperity range of 3 μm, and a molten alloyed punch with tungsten sulfide, calcium fluoride, and carbon (electron beam processing infinite product; EIP punch). The asperity range of the EIP punch was 2 μm. These rough asperities of the MH and EIP punches were determined by surface roughness tester (SurfTest SJ-400, Mitutoyo Co., Ltd., Kanagawa, Japan). As for the MH punch, the eventual surface was constituted of tungsten carbide. While, for the EIP punch, tungsten sulfide was used as an additive to promote alloying and then was decomposed during alloying process. Therefore, the eventual surface of the EIP punch was constituted of calcium fluoride, carbon, carbon fluoride, and slight amount of sulfur. Ibuprofen (Ibuprofen 25, listed in the Japanese Pharmacopoeia 16th Edition (JP16th), abbreviated as Ibu), lactose monohydrate (Pharmatose 200M, listed in JP16th, used as a filler), microcrystalline cellulose (Ceolus PH-102, listed in JP16th, used as a filler), and hydroxypropylcellulose (HPC-L, listed in JP16th, used as a binder) were kindly provided by BASF Japan Ltd. (Tokyo, Japan), DFE Pharma. (Tokyo, Japan), Asahi Kasei Chemicals Corp. (Tokyo, Japan), and Nippon Soda Co., Ltd. (Tokyo, Japan), respectively.

2.2. Granulation

Lactose monohydrate and microcrystalline cellulose were oven dried at 50°C for 12 h. Using a mixer (Fuji Medical Equipment Co., Ltd., Tokyo, Japan), 105 g of lactose monohydrate and 45 g of microcrystalline cellulose were mixed.
for 15 min. Ibu (150g) was then added and mixed for an additional 15 min. A total of 112.5 g of 5.0% w/w aqueous solution of HPC-L was added using a syringe (ss-10sz, Terumo Corporation, Tokyo, Japan), and the mixture was kneaded for 15 min. Granulation was performed using a rotating squeeze-type granulator with a sieve size of 0.8 mm (Hata Iron Work Co. Ltd., Kyoto, Japan). The granules were oven dried at 50°C for at least 12 h. After drying, they were sieved through a 1410 µm sieve and those granules that did not pass through a 350 µm sieve were collected. This process was repeated several times, and the resultant granules were mixed uniformly and subjected to experimental analyses.

2.3. Tablet preparation and determination of the pressure transmission ratio, ejection force, and scraper force

A total of 100 g of granules was put in a feeder. The tablets were prepared using a single punch tablet machine (TabAll N30-EX, Okada Seiko Co. Ltd., Tokyo, Japan) with a diameter of 8 mm (flat-faced punch). Tablet preparation was carried out under the relative humidity of 60±5% at room temperature. The weight of each tablet was 200 mg, the tableting speed was 10 tablets/min, and the tableting force was 3 kN. The pressure transmission ratio was calculated as the ratio of the maximum pressure of the lower punch to the maximum pressure of the upper punch. The ejection force (i.e. the force applied to the lower punch during tablet ejection) was measured by a 2 kN load cell. The scraper force during tableting was measured using a load cell mounted on the head of the feeder. Upper punch force, lower punch force, ejection force, and scraper force
data were recorded using DAATSU II software (Okada Seiko Co. Ltd., Tokyo, Japan). Two hundred tablets were prepared using each punch.

2.4. Determination of tablet hardness

Ten tablets were selected at random and the tablet hardness was determined by diametrical compression tests, which were performed using a hardness meter with a 300 N load cell (precision of 1 N, PC-30, Okada Seiko Co., Ltd., Tokyo, Japan) to accurately measure the maximal diametrical crushing force.

2.5. Determination of the amount of ibuprofen on the punch surface

After the tableting process, the powder adhering to the surface of the lower and upper punches was removed and dissolved in pH 6.8 phosphate buffer solution. The solution was then filtered through a membrane filter (0.45 μm) and absorbance was measured at 222 nm with a spectrophotometer (UV-mini, Shimadzu Corporation, Kyoto, Japan). The amount of Ibu was calculated from the absorbance of a standard solution.

2.6. Direct shear test

The direct shear test was performed using a powder shear tester (Tsutsui Scientific Instruments Co., Ltd., Tokyo, Japan) schematically as shown in Fig. 2. Metal plates used in this study were treated by alloying in the same manner as for the HCr, MH, and EIP punches. Each plate was inserted between a lower and upper cells and approximately 50 g of Ibu granules was placed in the upper cell. After flattening, the cell cap (5.4 g/cm²) was put on top of the Ibu granules,
subsequently a load of 142.6 g/cm² was applied to be compressed the powder layers. After that, the load of 142.6 g/cm² was discharged and then the substituted loads of 49.9–72.1 g/cm² were introduced to perform the direct shear test. The weight of the Ibu granules in the upper cell was then measured and the internal friction coefficient was determined from the relationship between vertical stress and shear stress.

2.7. X-ray photoelectron spectroscopy (XPS)

XPS measurement was performed for the EIP plate using a VG SCIENTIFIC ESCALAB 220i-XL spectrometer with a monochromatic Al Kα radiation ($hν = 1487$ eV) source. In this study, hexafluorobenzene was used as a standard substance in order to confirm the carbon-fluoride binding.

2.8. Imaging

A 10 mP digital camera (Canon IXY digital 110IS, Canon Inc., Tokyo, Japan) was used to take photographic images of the tablets and punches.

2.9. Statistics

Statistical analyses were performed using the Student $t$-test. A probability value of $p<0.05$ was considered to indicate statistical significance.
3. Results and discussion

3.1. Evaluation of the anti-sticking properties of the MH and EIP punches by visual observation and Ibuprofen adherence

When the tablets were prepared using a single punch tablet machine, an obvious crack was observed on the surface of tablets prepared by the HCr punch compared with only a slight crack on the surface of tablets prepared by the MH and EIP punches (Fig. 3). In this experiment, no lubricant was added to the granules. Despite this, the pressure transmission ratio was comprehensively high at 87.1–88.9%, and the ejection force was comprehensively low at 20.3–28.6 N for each punch and there were no significant differences between the HCr, MH, and EIP punches, showing good compaction values against Ibu granules (Table 1). In addition, tablets with a hardness of 118, 108 and 107 N could be prepared by the HCr, MH and EIP punches, respectively (Table 2). Previously, the compression speed and ejection process from a die have been reported to affect the sticking phenomenon and the value of scraper force (Waimer et al., 1999). In this study, compression speed was the same in the tableting experiments used for the HCr, MH and EIP punches. In addition, good compaction properties were also observed. Therefore, the following results regarding the amount of Ibu adhering to the punch surface and the scraper force were considered to be directly affected by the differences in surface properties of these punches.

Figure 4a shows the lower punch of the HCr, MH and EIP punches before and after tableting 200 tablets. In accordance with the results shown in Fig. 3, the amount of powder adhering to the punch surface was lowest for the EIP punch, followed by the MH and HCr punches. The same results were found for
the surfaces of the upper punches (data not shown). A significantly lower
amount of Ibu had adhered to the lower punch of both the MH and EIP punches
(0.06 mg) compared with the HCr punch (0.176 mg; \( p<0.05 \)) (Fig. 4b).

3.2. Evaluation of the anti-sticking properties of the MH and EIP punches by
scraper force

As an indicator of the sticking phenomenon, changes in the scraper force
up to the 200th tablet were determined as shown in Fig. 5. Basically, the scraper
blade is a part of tablet machine, the role of which is to discharge tablets
outward. At the moment, the lateral side of tablet is forced to be hit by the
scraper blade. Namely, the value of scraper force is the horizontal force exerted
to remove the tablet from the surface of lower punch. When the Ibu granules
were compressed with the HCr punch, the scraper force increased to 2.60–4.28
N immediately after the start of tableting. By contrast, the scraper force for the
MH punch increased gradually, with values of 0.54–1.64 N for the last 10
tablets. Almost all scraper forces for the EIP punch were zero throughout the
tableting process, with end values of 0.42–1.33 N. Shibata et al. reported that
use of the common lubricant magnesium stearate significantly decreased the
scraper force from 5.07 N to 1.03 N, thereby preventing sticking when the solid
dispersion of ibuprofen was compressed using a single punch tableting machine
(Shibata et al., 2006). In this study, the tableting speed was almost the same as
that used by Shibata et al., and the values of our scraper force are in accordance
with those of Shibata et al., even if in the absence of lubricant. This
demonstrates that the MH and EIP punches can significantly reduce the sticking
problem during the manufacturing of Ibu tablets. Schumann and Searle previously reported that a punch with a more pitted surface was associated with fewer sticking problems than one with a smooth surface, because the microscopic pits in the rougher punch surface acted as loci that break the adhesive force between tablet and punch (Schumann and Searle, 1992). In addition, Roberts et al. also demonstrated that a rougher punch surface with a maximum range of 3.78 µm showed less sticking than smoother punch surfaces with maximum ranges of 0.44 µm and 0.19 µm (Roberts et al., 2003). Generally, rough asperity of punch surface results in a decrease in contact area between the punch surface and the powders. Therefore, this suggests that a rougher surface might be associated with the anti-sticking properties of the MH and EIP punches.

3.3. Characterization of the surfaces of the punches and metal plates

As described above (section 3.2), a slight difference in the scraper profile was observed between the MH and EIP punches (Fig. 5). To understand this difference, the internal friction coefficients of the HCr, MH, and EIP punches were investigated by the direct shear test. Table 3 shows the internal friction coefficient of a metal plate treated in the same alloying manner as the HCr, MH, and EIP punches. No significant difference was observed between these alloying plates; however, the internal friction coefficient between the Ibu granules and EIP plate was the lowest, followed by those of the MH and HCr plates. Figure 6 shows the result of the XPS for the EIP plate. Two peaks were observed around 685 eV derived from F1s spectrum of calcium fluoride and 689 eV derived from
F1s spectrum of carbon fluoride of binding energy, respectively. Both of them are well-known substances with low friction property. In addition, the ratio of carbon fluoride was found to be equal to that of calcium fluoride since the intensities for both substances were the same. In the previous studies, it has been reported that calcium fluoride exhibited the low friction property at only high temperatures such as from 400°C to 950°C, and using the cobalt-based disc coated with calcium fluoride and alumina ball, the friction coefficient of calcium fluoride has been found to be 0.4 at a temperature of 500°C (Jin et al., 1998, Pauleau et al., 1998). On the contrary, that of carbon fluoride has been found to be 0.08 using the steel disc coated with carbon fluoride and steel ball (Thomas et al., 2006), suggesting that carbon fluoride shows lower friction coefficient. Therefore, for the EIP punch, although the proportion of carbon fluoride was equal to calcium fluoride, carbon fluoride might be mainly involved in the anti-sticking property of the EIP punch compared to calcium fluoride.
4. Conclusion

Sticking is a serious tableting problem that occurs during the tablet manufacturing process, resulting in deterioration in tablet productivity and appearance. We originally designed the MH and EIP punches to prevent the sticking phenomenon, and have demonstrated here for the first time, through a quantitative analysis of the scraper force in the tableting process, that these punches show superior anti-sticking properties against Ibu tablets to the HCr punch. In addition, for the MH punch, the anti-sticking property could be attributed to the rough asperity, and that for the EIP punch could be attributed to the rough asperity as well as lower internal friction coefficient of the punch surface derived from the carbon fluoride. It was also found that the EIP punch showed superior anti-sticking property among the punches used in this study.

The present study also suggests a possibility that the alloying technique might be able to resolve other manufacturing problems involving the adhesion of powder onto a metal surface. For instance, in the tablet manufacturing process, fine particles might adhere to the turntable of the rotary tableting machine because of high friction force, resulting in a reduction in productivity. Similarly, powder has been found to adhere to stainless steel tamping pins in a tamp-filling machine during capsule filling (Podczeck, 1999). Although several adhesion forces occur between particles and surfaces, such as van der Waals, capillary, and electrostatic forces, the MH and EIP alloying techniques can improve adhesion problems. Further investigations are now required regarding the anti-electrostatic properties of these techniques and their application.
Acknowledgments

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References


332 Roberts, M., Ford, J.L., MacLeod, G.S., Fell, J.T., Smith, G.W., Rowe, P.H., Dyas, A.M., 2004a. Effect of lubricant type and concentration on the


Table Captions

Table 1. Tableting properties of Ibu granules using the HCr, MH, and EIP punches.

Table 2. Tablet hardness prepared by the HCr, MH, and EIP punches.

Table 3. Internal friction coefficient between Ibu granules and the HCr, MH, or EIP plates.
Table 1.

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<th>Tableting properties</th>
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<td>Pressure transmission ratio (%)</td>
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<td>88.9±0.5</td>
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<td>Ejection force (N)</td>
<td>24.2±14.6</td>
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Data expressed as mean ± S.D. (n=3).

Table 2.

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<td>Table hardness (N)</td>
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Data expressed as mean ± S.D. (n=10).

Table 3.

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<td>Internal friction coefficient</td>
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Data expressed as mean ± S.D. (n=3).
Figure Legends

Figure 1. Schematic diagrams and photographs of punch surface treatments. (a) Surface treatment schematic of MH punch. (b) MH punch photograph. (c) Surface treatment schematic of EIP punch. (d) EIP punch photograph.

Figure 2. Diagram of direct shear tester.

Figure 3. Photographs of tablets after 200th compression using different punches. (A) HCr, (B) MH, and (C) EIP punches.

Figure 4. Photographs of lower punches before and after tableting (a) and amount of ibuprofen adhering to the lower punch surfaces (b). (A) HCr, (B) MH, and (C) EIP punches. Columns represent the average value obtained from three determinations (± S.D.). *, p<0.05, compared with the HCr punch group.

Figure 5. Change in scraper force during the tableting process. Points represent the average value obtained from three determinations. HCr, closed diamond; MH, open circle; EIP, closed triangle.

Figure 6. XPS spectra in the F1s region for the surface of the EIP plate.
Fig. 1

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a)
Electrode for MH alloying
MH alloying
Micro peeling
Burnishing
MH punch

b)

Layering of metal powder
Irradiation of electron beam
Removal of impurities
Micro peeling
EIP punch

c)

Layering of metal powder
Irradiation of electron beam
Removal of impurities
Micro peeling
EIP punch

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Fig. 3

A) HCr  B) MH  C) EIP

Tablet surface

Tablet side
Fig. 4

a) A) HCr  B) MH  C) EIP
Before

After

b) Adhesion amount of Ibuprofen (mg/punch)

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<tr>
<th></th>
<th>HCr</th>
<th>MH</th>
<th>EIP</th>
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<tr>
<td></td>
<td>0.20</td>
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* *
Fig. 5

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Fig. 6

Intensity (Arb. Units)

Binding energy (eV)

C₆F₆

CF bonding

CaF₂

EIP punch

694 692 690 688 686 684 682 680